Remarks

Claims 1-17 are pending in the present application. Claims 1-11 and 13 were rejected under 35 U.S.C. § 103(a). Applicants respectfully request reconsideration of the application, withdrawal of all objections, and allowance of the application in view of the amendments and remarks below.

The Amendments to the Claims

Claim 1 has been amended to include the word "composition" to provide antecedent basis for the term in Claims 2, 3 and 5. Claims 1, 5-7, 13, 14, 16 and 17 have been amended to replace "the" with "said" to be consistent with the remaining claims. These amendments are made to clarify the claims and are supported by the specification.

The Rejection under 35 U.S.C. §103(a)

The Examiner has rejected Claims 1-11 and 13 under 35 U.S.C. § 103(a) as being unpatentable over Howell et al. (5,743,251). In support of this rejection, the Office Action states that "Howell et al. teaches aerosols formed by supplying a material in liquid form to a tube and heating the tube such that the material volatizes and expands out of an open end of the tube . . . [and] combines with ambient air such that volatized material condenses to form the aerosol." Office Action at 2. The Office Action further states that "[t]he aerosols have an average mass median particle diameter of less than 2 microns to facilitate deep lung penetration." *Id.* at 2-3.

The Office Action acknowledges that Howell et al. "does not state the method steps for the preparation of a condensation aerosol as recited in the instant claims" but asserts that "the modifications would have been obvious to one of ordinary skill in the art." *Id.* at 3. The Office Action states that Howell et al. "provides sufficient disclosure for one of ordinary skill in the art to make and use the invention as claimed" and that "[t]he formation of particles with a mass median diameter of less than 2 reads on the limitation of 0.1 micron." *Id.*

Applicants respectfully disagree in view of the elements of the pending claims and the disclosure of Howell et al. As Applicant pointed out in the Response document filed July 27, 2005, according to the method disclosed in Howell et al., a material in liquid form is supplied to

a tube having an open end. The liquid material filling the tube is heated such that the liquid material volatilizes and expands out of the open end of the tube (col. 2, lines 18-25). This liquid supply arrangement allows the aerosol generator of Howell et al. to provide uninterrupted, continuous production of the aerosol (col. 7, lines 41-42). Howell et al. does not disclose or suggest depositing a drug on a substrate, as required by Claim 1 of the present application. Nor does Howell et al. provide sufficient disclosure or motivation for one of ordinary skill in the art to make and use the invention as claimed.

With respect to Applicant's foregoing arguments, the Office Action states that Howell et al. teaches "placing the drug in a tube, and it is considered that a 'tube' reads on 'a substrate'" and that the claims "do not specify any form for the drug, thus Howell's 'liquid' also reads on the instant 'drug'" (*Id.* at 6).

In response, Applicant states that Howell et al. does not disclose or suggest "depositing" a drug composition on a substrate, as required by the present claims. Howell et al. describes supplying a drug in liquid form to fill a tube, it does not teach or suggest "depositing" a liquid on the tube. Howell et al. recognizes the distinction. The "depositing" language cited by the Office Action (*Id.* at 3) relates to depositing a thin platinum layer on the tube for use as a heater. See col. 3, lines 60-64 and col. 4, lines 14-21 (listing a number of techniques for depositing a thin layer heater on the tube, including sputter deposition, vacuum evaporation, chemical deposition and electroplating).

Additionally, as Applicant pointed out in its previous Response, Howell et al. does not enable the preparation of a condensation aerosol having a mass median aerodynamic diameter of less than 0.1 microns, as required by Claim 1 of the present invention, or teach the importance of this size range. While Howell et al. states generically that "[i]n drug delivery applications, it is typically desirable to provide an aerosol having average mass median particle diameters of less than 2 microns to facilitate deep lung penetration" (col. 2, lines 1-4), Howell et al. does not teach one of skill in the art how to prepare an aerosol with a mass median aerodynamic diameter of less than 0.1 micron. Indeed, when discussing the aerosol generator, and the aerosols that can be obtained therewith, Howell et al. refers to the mass median aerodynamic diameter as being between 0.2 and 2 microns. *See* col. 7, lines 44-45 ("It will be appreciated that a liquid supply arrangement such as the above-described syringe pump 141 is well suited to supply liquid at a

rate of 1 milligram/second or greater, as needed, and that, provided a sufficiently powerful heater 127 is provided, an aerosol may be continuously produced at a rate of 1 milligram/second or greater, which is understood to be a much greater rate of delivery of particles in *sizes between 0.2 and 2 microns* mass median particle diameter than is available with conventional aerosol drug delivery systems.") (emphasis added); *see also*, col. 2, lines 7-10 ("Most known aerosol generators suited for drug delivery are incapable of delivering such high flow rates in the *0.2 to 2.0 micron size range.*") (emphasis added).

Similarly, the Examples provided in Howell et al. do not provide any support for the preparation of a condensation aerosol having a mass median aerodynamic diameter of less than 0.1 microns. The examples reflect various runs performed with the aerosol generator of Howell et al. In each run, one or more parameters of the aerosol generator or liquid material were varied in ways expected to affect the aerosol mass median particle diameter (col. 9, lines 27-32) and an effort was made to optimize the mass median particle diameter to the smallest diameter. *See* col. 13, lines 65-66 ("As in the case of the 0.1 mm tube, the fluid feed rates were varied *in an effort to optimize the mass median particle diameter to the smallest diameter.*") (emphases added). Nevertheless, none of the 48 reported runs produced aerosols having a mass median aerodynamic diameter less than 0.1 microns. In fact, the smallest mass median aerodynamic diameter achieved was 0.35 microns (Table IV), a value more than three-fold higher than the upper limit of the size range recited in the present claims.

Additionally, Howell et al. does not recognize the importance of an aerosol having a mass median aerodynamic diameter less than 0.1 microns relative to the 0.2 to 2 micron range disclosed in Howell et al. The claimed mass median aerodynamic diameter of less than 0.1 microns is important for effective drug delivery through diffusion and achieves different results relative to the 0.2 to 2 micron range disclosed in Howell et al.

Applicants not only enable one to make aerosols having a mass median aerodynamic diameter of less than 0.1 microns, but also teach the importance of this size range. Applicants specifically teach that ultra fine particles of less than 0.1 microns are sufficiently small so as to diffuse in the lung in a timely manner while, on the other hand, particles "between 0.1 and 1 micron in size, are too small to settle onto the lung wall and too massive to diffuse to the wall in a timely manner. Thus, a significant number of such particles are removed from the lung by

exhalation, and . . . are not involved in treating disease." U.S. patent application Serial No. 10/057,197 at page 5, lines 1-8 (incorporated by reference in the present application).

With respect to Applicant's foregoing arguments, the Office Action states that "a disclosure of 'less than 2 microns' encompasses 'less than 0.1 micron'" (*Id.* at 6). Furthermore, the Office Action states that "optimization of ranges is a) obvious to one of ordinary skill in the art and b) NOT a support for patentability. Absent a showing of the criticality of a smaller particle size, it is considered that the prior art renders it obvious" (*Id.*).

In response, Applicant states that Howell et al. does not recognize that, within the mass median aerodynamic diameter range of "less than 2 microns," particle size affects whether effective drug delivery is possible. Applicants specifically teach the desirability of "ultra fine" particles (0.01 to 0.1 micron) over "middle size" particles (0.1 to 1 micron). The "ultra fine" particles are sufficiently small to diffuse to the lung wall and provide "efficient and effective systemic delivery through the lung." By contrast, the "middle size" particles are too large to diffuse to the lung wall in a timely manner and a significant number of such particles are removed from the lung by exhalation and thus are not involved in treating disease. (U.S. patent application Serial No. 10/057,197 at page 5, lines 1-8) (incorporated by reference in the present application). Howell et al. does not recognize these distinctions. In fact, Howell et al. states that, for aerosols intended for inhalation, the mass median particle diameter of the aerosol is "preferably between 0.2 and 2 microns, and more preferably between 0.5 and 1 microns" (col. 9, lines 12-18). Thus, a significant number the particles in Howell et al.'s "preferred" ranges are of a size that is too large to diffuse to the lung wall in a timely manner. Indeed, by pointing to these undesirably large particles as "preferred," Howell et al. teaches away from the desirable size range of "less than 0.1 microns" of the present claims.

Furthermore, Howell et al. fails to teach one of skill in the art how to obtain an aerosol with a mass median aerodynamic diameter range of "less than 0.1 microns." The smallest mass median aerodynamic diameter produced by the device of Howell et al. was 0.35 microns (col. 13, line 50; Table IV). Nor does Howell et al. provide any guidance on how to prepare an aerosol with a mass median aerodynamic diameter less than 0.1 microns. Indeed, Howell et al. provides no evidence whatsoever that the disclosed device is even capable of producing such an aerosol. Thus, Howell et al. does not provide one of skill in the art with the tools necessary to "optimize

the range" with respect to aerosols having a mass median aerodynamic diameter less than 0.1 micron.

By contrast, Applicant's specification contains a detailed discussion of producing an aerosol comprised of particles within a desired size range. See ¶¶ [0121]-[0136]. Additionally, Applicant's specification includes a number of examples of aerosols having a mass median aerodynamic diameter less than 0.1 microns. See, e.g., ¶ [0171] (0.08 microns); Table 2 (0.071 microns); Table 4 (0.065 microns); Table 5 (0.092 microns).

According to the MPEP § 2143, "to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references (or references when combined) must teach or suggest all the claim limitations." Obviousness cannot be established by combining teachings in the prior art, absent some teaching or suggestion in the prior art that the combination be made (*In re Stencel* 828 F. 2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987); *In re Newell* 891 F. 2d 899, 13 USPQ2d 1248 (Fed. Cir. 1989)).

As the Howell et al. reference does not teach or suggest all the elements of Claim 1, Howell et al. does not make obvious the claimed invention. Moreover for the same reason, there would be no motivation to modify the aerosol generator of Howell et al. to achieve the presently claimed invention. Furthermore, Howell et al. does not enable the preparation of a condensation aerosol having a mass median aerodynamic diameter of less than 0.1 microns, as required by Claim 1, or teach the importance of this size range. Thus, Howell et al. does not make obvious the claimed invention. As Claims 2-17 depend from Claim 1, Claims 2-17 are not obvious for the same reasons.

Double Patenting

Claims 1-17 were rejected under the judicially created doctrine of obviousness-type double patent as being unpatentable over all claims of U.S. Patent Nos. 6,776,978, 6,716,417, 6,797,259, 6,740,309, 6,743,415, 6,737,042, 6,814,955, 6,805,584, 6,716,415, 6,803,031, 6,759,029, 6,737,043, 6,740,308, 6,740,307, 6,716,416, 6,783,753, 6,780,400, 6,780,399, 6,805,853, and

6,814,954. Office Action at 4.

Also, Claims 1-17 were provisionally rejected under the doctrine of obviousness-type double patenting as being unpatentable over claims of copending Application Nos. 10/815,527, 10/816,492, 10/768,220, 10/766,574, 10/813,721, 10/767,115, 10/816,567, 10/766,279, 10/766,641, 10/814,998, 10/718,982, 10/769,157, 10/769,197, 10/769,051, 10/768,205, 10/766,647, 10/792,013, 10/792,012, 10/766,634, 10/766,566, 10/768,293, 10/791,915, and 10/775,586. *Id.* at 4.

When the present claims are determined to be patentable, Applicants will submit Terminal Disclaimers with regard to U.S. Patent Nos. 6,776,978, 6,716,417, 6,797,259, 6,740,309, 6,743,415, 6,737,042, 6,814,955, 6,805,584, 6,716,415, 6,803,031, 6,759,029, 6,737,043, 6,740,308, 6,740,307, 6,716,416, 6,783,753, 6,780,400, 6,780,399, 6,805,853, and 6,814,954 and copending Application Nos. 10/815,527, 10/816,492, 10/768,220, 10/766,574, 10/813,721, 10/767,115, 10/816,567, 10/766,279, 10/766,641, 10/814,998, 10/718,982, 10/769,157, 10/769,197, 10/769,051, 10/768,205, 10/766,647, 10/792,013, 10/792,012, 10/766,634, 10/766,566, 10/768,293, 10/791,915, and 10/775,586. Applicants believe that this will address the Examiner's concerns and respectfully request reconsideration of the application, withdrawal of all rejections, and allowance of the application in view of these actions and remarks.

Conclusion

The Applicants appreciate the Examiner's careful and thorough review of the application and submit that the Examiner's concerns have been addressed by the amendments and remarks above. The Applicants accordingly request the Examiner to withdraw all rejections and allow the application. In the event the Examiner believes a telephonic discussion would expedite allowance or help to resolve outstanding issues, prosecution of the application, then the Examiner is invited to call the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

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